species election may be withdrawn pending the response to the rejection under 35 U.S.C. § 103, Applicants have not amended Claims 10 and 11 to remove the non-elected species. Applicants respectfully defer making such an amendment, if still necessary, until prosecution of the remaining issues is closed.

(b) The Examiner has objected to Claim 41 as being improperly amended for not containing brackets around the term "or" and for not containing an underline for the "/" inserted into the claim. Applicants note that the omission of the term "or" and the insertion of a "/" is an apparent typographical error in the reproduction of Claim 41 in the last Amendment and Response. Therefore, for purposes of clarification, Applicants have presented Claim 41 as a "reiterated" claim, assuming that the only entered amendments were those that were presented in proper format pursuant to 37 CFR § 1.121.

Rejection of Claim 11 Under 35 U.S.C. § 112, Second Paragraph:

The Examiner has maintained the rejection of Claim 11 under 35 U.S.C. § 112, second paragraph, contending that it is still not clear what homology is needed to encompass a homologue described in the claims.

To expedite prosecution, Applicants have amended Claim 11 to remove the language found objectionable by the Examiner and to simply recite that the targeted immune system inhibitor is produced by a microorganism. As set forth in the specification on page 6, lines 7-22, infectious microorganisms are known in the art to produce molecules that serve to suppress the host immune response during the initial stages of infection, to provide advantage to the microbe, and to enhance the virulence and chronicity of the infection (i.e., are immune system inhibitors). The specification provides citations to publications that describe such immune system inhibitors that are produced by microorganisms.

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claim 11 under 35 U.S.C. § 112, second paragraph.

Rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42, and 50-56 Under 35 U.S.C. § 103:

The Examiner has maintained the rejection of Claims 1-3, 5, 10-27, 34, 37-38, and 40-42 and has newly rejected Claims 50-56 under 35 U.S.C. § 103, contending that these claims are unpatentable over Lentz (U.S. Patent No. 4,708,713) and further in view of Selinsky et al.

(*Immunology* 94:88-93, 5/1998) and Marakovsky et al. (U.S. Patent No. 6,017,527). The Examiner contends that Lentz does teach separation of blood into the plasma component which is a cellular and acellular separation. The Examiner additionally asserts that one cannot show non-obvious by attacking the references individually where the rejections are based on a combination of references. With regard to Selinsky et al., the Examiner contends that this reference teaches that the soluble tumor necrosis factor receptor type I is removed by Ultraphoresis[sic] and thus, with the knowledge of Lentz, one would know that soluble immune system inhibitors can be removed from the acellular components of blood. With regard to Marakovsky, the Examiner submits that this reference is cited for providing a teaching of immobilized antibody on surfaces such as beads and the antibody removes cells that contain a specific antigen. The Examiner finally states that any judgment on obviousness is in a sense necessarily a reconstruction based upon hindsight reasoning, but so long as it takes into account only knowledge which was within the level of ordinary skill and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper.

Applicants traverse the rejection of Claims 1-3, 5, 10-27, 34, 37-38, 40-42, and 50-56 under 35 U.S.C. § 103. As discussed in the telephone interview of February 6, Applicants maintain their position that the combination of references cited by the Examiner does not teach or suggest the present invention as claimed. Specifically, Applicants maintain the position as set forth in the previous Amendment and Response (filed November 1, 2000) that none of the references, alone or in combination, teaches the use of a specific binding partner to *selectively and specifically* remove targeted components from the acellular component of whole blood for the purpose of producing an altered bodily fluid with enhanced immune stimulatory properties. Moreover, Applicants submit that the arguments presented with regard to the cited references in the November 1 Amendment and Response demonstrated deficiencies in the combination of references *as a whole*; therefore, Applicants maintain their position that the combination of references does not teach or suggest all of the claim limitations nor does the combination provide the requisite motivation to arrive at the present invention.

In support of Applicants position, and as suggested by the Examiner in the February 6 telephone interview, enclosed herewith is a Declaration under 37 CFR 1.132 of Dr. Mark D. Howell and Dr. Cheryl L. Selinsky. Drs. Howell and Selinsky are coinventors of the present application, and have provided comments in support of Applicants' position regarding the references of Lentz and Selinsky et al. This Declaration was not earlier presented because it was not until the telephone

interview of February 6 that Applicants were made aware of the Examiner's suggestion to provide such a document.

With regard to the Examiner's comment that Lentz does disclose the possibility of separation of blood into a plasma component and a cellular component, Applicants again submit that Lentz also discourages the separation of plasma from whole blood (see November 1, 2000 Amendment and Response) and therefore, at best, the teachings of Lentz are ambiguous on this issue. Moreover, as discussed in the Declaration under 37 CFR 1.132 (See paragraph 3, discussion of Lentz), no advantage is obtained in the Lentz process by separating cellular and acellular components of whole blood, whereas there are significant advantages of such a separation in the presently claimed method, as discussed in detail in the Declaration. Since Lentz is, at best, ambiguous on the point of separating plasma from whole blood, and further, does not obtain any advantage from such separation, Applicants submit that neither Lentz, nor the other cited references, nor the Examiner, has provided any motivation to combine the ambiguous discussion in Lentz with the other cited references in the manner suggested by the Examiner.

As noted, the Examiner contends that Selinsky et al. teach that the soluble TNFRI is removed by Ultraphoresis[sic] and that, with the knowledge of Lentz, one would know that soluble immune system inhibitors can be removed from whole blood. Applicants again assert that Selinsky et al., alone or in combination with Lentz and/or Marakovsky, do not teach the use of a binding partner that selectively binds to an immune system inhibitor to selectively remove such an inhibitor from the acellular portion of a biological fluid, nor any method, including any *ex vivo* method, for contacting an acellular portion of a bodily fluid such as blood with a binding agent that selectively binds to a targeted immune system inhibitor such that the inhibitor is removed from the acellular portion, and then combining the altered acellular portion with the cellular portion of the fluid and returning the fluid to the animal from which it was obtained. At best, Applicants submit that Selinsky et al. can be viewed as no more than an invitation to experiment. Moreover, as set forth in the Declaration under 37 CFR 1.132 (See paragraph 3, discussion of Selinsky et al.), Applicants assert that at the time of the present invention, one of skill in the art, when presented with an invitation to manipulate the effects of a soluble protein, would look to a variety of conventional approaches to remove or manipulate the effects of that soluble protein *in vivo*, because such approaches are the most clinically desirable means of treating a patient. The *ex vivo* approach claimed in the present application is not conventional, and indeed, would be much less likely to be considered because conventionally, it

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would be viewed as less direct, more expensive, and more invasive than *in vivo* approaches, as discussed in the Declaration.

Therefore, the combination of Lentz and Selinsky et al. fail to teach or suggest the use of a specific binding partner to *selectively and specifically* remove targeted components from the acellular component of whole blood for the purpose of producing an altered bodily fluid with enhanced immune stimulatory properties. Since, by the Examiner's admission, Marakovsky is cited only for the teaching of immobilized antibody on surfaces such as beads for the purpose of removing cells that contain a specific antigen, this reference does not make up for the deficiencies of the combination of Lentz and Selinsky et al. as discussed above. Therefore, the combination of references fails to teach the elements of the claimed invention, and further, fails to provide the requisite motivation to make and use the claimed method.

In view of the remarks above and in the attached Declaration under 37 CFR 1.132, Applicants again assert that the only suggestion for the Examiner's combination of the teachings in the cited references improperly stems from the Applicants' own disclosure and not from the cited references themselves. Applicants submit that none of the references, alone or in combination, provide an impetus necessary to cause one skilled in the art to combine the teachings of the references in the way the Examiner has done.

In view of the foregoing remarks, Applicants respectfully request that the Examiner withdraw the rejection of Claims 1-3, 5, 10-27, 34, 37-38, and 40-42 and the newly rejected Claims 50-56 under 35 U.S.C. § 103.

Rejection of Claims 10 and 12-13 Under 35 U.S.C. § 112, Second Paragraph:

(a) The Examiner has rejected Claim 10, contending that there is insufficient antecedent basis for the limitation "immune system inhibitor" in Claim 1. Applicants have amended Claim 10 to insert the term "targeted" before this phrase, thus correcting the issue of proper antecedent basis in Claim 1.

(b) The Examiner has rejected Claims 12-13 as being indefinite for the recitation of "naturally binds." The Examiner asks whether the phrase means a binding partner that is the binding partner found naturally in a cell, or any binding partner that would "naturally" bind to the inhibitor.

Applicants respectfully refer the Examiner to page 16, line 26, to page 17, line 5 of the specification, where it states:

> The binding partner can be one which naturally binds the targeted immune system inhibitor. For example, tumor necrosis factor α or β can be used as a binding partner for sTNFRI. Alternatively, other binding partners, chosen for their ability to selectively bind to the targeted immune system inhibitor, can be used.

Applicants submit that from this description, it is clear that the meaning of the phrase "naturally binds" is the binding partner that is found naturally in a cell, since the given example is an example of ligand/receptor partners that occur in nature, and since the alternative given is a partner that is chosen for its ability to selectively bind to the targeted immune system inhibitor, and includes fragments of the natural partner, antibodies, peptides, etc. However, to clarify what is meant by the recited phrase, Applicants have amended Claims 12 and 14 to recite that the binding partner is a binding partner "to which the targeted immune system inhibitor binds in nature." Applicants submit that this phrasing is merely a rewording of the above-referenced passage at pages 16-17, wherein the meaning of the passage remains intact (MPEP 2163.07(I)).

In view of the foregoing discussion, Applicants respectfully request that the Examiner withdraw the rejection of Claims 10 and 12-13 under 35 U.S.C. § 112, second paragraph.

Applicants have attempted to address all of the Examiner's concerns in the August 18 Office Action. In the event that the Examiner has any questions regarding Applicants' position, the Examiner is invited to contact the below-named agent at (303) 863-9700.

Respectfully submitted,

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